REMARKS

Claim amendments

Claims 7, 12-14, 27, 44 and 60 have been previously canceled. Claims 1, 9, 10 and 11 have been amended to more clearly indicate that the DNA fragments are combined with a DNA microarray comprising one or more sequences complementary to one or more intergenic regions of genomic DNA of the cell *wherein each one or more sequences is located at a particular spot on the DNA microarray and the one or more intergenic regions are upstream of transcribed regions of the genomic DNA* (Claim 1, step f; Claim 9, step g; Claim 10, step f; and Claim 11, step f). Support for the amendment "wherein each one or more sequences is located at a particular spot on the DNA microarray" can be found, for example, as follows:

> Finally, the labeled DNA was hybridized to a DNA microarray containing spots representing all or a subset (e.g., a chromosome or chromosomes) of the genome. The fluorescent intensity of each spot on the microarray relative to a non-immunoprecipitated control demonstrated whether the protein of interest bound to the DNA region located at that particular spot (specification, page 17, lines 9-13);

and

> we PCR amplified and printed 6361 spots, representing all of the known intergenic regions in the yeast genome (specification, page 63, line 26 - page 64, line 1).

Support for the amendment "and the one or more intergenic regions are upstream of transcribed regions of the genomic DNA" can be found, for example, as follows:

> The intergenic regions present on the array were assigned to the gene or genes found transcriptionally downstream (specification, page 40, lines 17-19 and page 85, lines 10-11).

No new matter has been added.

Claim interpretation

The Examiner states that the term "intergenic" includes transcribed regions of a gene (Office Action, page 2). In addition, the Examiner maintains the broad interpretation of the term "DNA microarray" (Office Action, page 3).

Applicants respectfully disagree. Nevertheless, in order to more clearly define the invention, the claims have been amended to indicate that the intergenic regions are upstream of transcribed regions of the genomic DNA and that the one or more sequences are located at a particular spot on the DNA microarray.

Finally, the Examiner states that since any DNA sequence is a "consensus" sequence of itself, the term imposes any specific structure on the claims.

Applicants respectfully disagree and respectfully request that the Examiner provide support for the statement that "any DNA sequence" may be deemed a consensus sequence of itself (Office Action, page 3).

Rejection of Claims 1-6, 8, 10, 11, 17-22, 39-43, 48-53, 56-59, 61, 64-68, 71-76 and 78-84 under 35 U.S.C. §102(b)

Claims 1-6, 8, 10, 11, 17-22, 39-43, 48-53, 56-59, 61, 64-68, 71-76 and 78-84 are rejected under 35 U.S.C. §102(b) "as being anticipated by Orlando et al." (Office Action, page 4). The Examiner interprets the term "microarray" broadly, and thus, is of the opinion that Orlando *et al.* "still reads on the claims" including new claims 71-86 (Office Action, page 19).

Applicants respectfully disagree. Nevertheless, as noted above, Claims 1, 9, 10 and 11 have been amended to indicate that the one or more sequences on the DNA microarray are located at a particular spot on the DNA microarray. In contrast, Orlando *et al.* "devised a PCR and hybridization strategy that allows the identification of all binding sites of ***a particular protein*** within a genomic region of interest" wherein "DNA associated with specifically immunopurified chromatin is amplified by PCR and used as a probe in Southern analysis of a given genomic region" (Orlando *et al.*, page 205, column 2).

As for newly added Claims 71-86, Orlando *et al.* do not teach or even suggest that the PCR and hybridization strategy can be used to identify regions across a genome of a cell where binding of ***DNA proteins*** occur.

Orlando *et al.* do not anticipate Applicants' claimed invention, particularly as amended.

Rejection of Claims 1-6, 8-11, 15-22, 25, 26, 28-36, 39-53, 56-59, 61-68 and 71-84 under 35 U.S.C. §102(e)

Claims 1-6, 8-11, 15-22, 25, 26, 28-36, 39-53, 56-59, 61-68 and 71-84 are rejected under 35 U.S.C. §102(e) "as being anticipated by Mercola (U.S. Patent 6,410,233)" (Office Action, page 6). Noting Applicants' position that Mercola *et al.* "is deficient since Mercola discusses the use of cDNA arrays", the Examiner states that Figure 11 of Mercola *et al.* "demonstrates that Mercola uses sequences outside the open reading frame" and that "the term 'intergenic' is extremely broad and simply reads on any region between two genes" (Office Action, page 19).

Applicants respectfully disagree. Figure 11 of Mercola is "the complete sequence of a clone identified using the methods of the present invention" (Mercola *et al.*, column 2, lines 27-28). Mercola *et al.* performed a gel shift assay "using a probe derived from the 5' region" of the clone, which was outside the open reading frame of the clone, and included a putative Egr-1 binding site (Mercola *et al.*, column 2, lines 30-32 and column 22, lines 1-2). However, Mercola *et al.* do not teach or suggest using this region that is outside the open reading frame on a DNA microarray to identify ***nucleic acid molecules corresponding to genes*** regulated by a transcription factor. Mercola *et al.* clearly do not teach use of an intergenic region that is upstream of transcribed regions of the genomic DNA to identify ***nucleic acid molecules corresponding to genes*** regulated by a transcription factor. As noted in the previously filed Amendment, Mercola *et al.* teach "methods for the identification of ***nucleic acid molecules corresponding to genes*** regulated by a transcription factor" using DNA fragments isolated according to the invention, to "probe ***cDNA arrays*** on a matrix" (Mercola *et al.*, abstract and Figure 1, emphasis added). As noted in Figure 1 of Mercola *et al.*, "[l]ocation of hybridized cDNA identifies the ***gene target***.

The Examiner notes that the term "intergenic" is "extremely broad and simply reads on any region between two genes" (Office Action, page 19), and that the "5' sequence shown by Mercola is between two genes and therefore meets the limitation of the claims" (Office Action, page 20). However, Mercola *et al.* do not teach or suggest using this 5' region outside the open reading frame on a DNA microarray to identify ***nucleic acid molecules corresponding to genes*** regulated by a transcription factor. Nevertheless, in order to more clearly define Applicants'

invention, the claims have been amended to indicate that the intergenic regions are upstream of transcribed regions of the genomic DNA.

Mercola *et al.* do not anticipate Applicants' claimed invention, particularly as amended.

Rejection of Claims 9, 15, 16, 25, 26, 28-36, 46, 47, 62, 63, 77 and 78 under 35 U.S.C. §103(a)

Claims 9, 15, 16, 25, 26, 28-36, 46, 47, 62, 63, 77 and 78 are rejected under 35 U.S.C. §103(a) as being unpatentable over Orlando *et al.* in view of Hacia *et al.* (Office Action, page 9). Noting Applicants' position that the Southern analysis of Orlando is not equivalent to the microarray analysis of Applicants' claimed invention, the Examiner states that "the term 'microarray' is not limited to any specific format" and that "there is no structural element of the claim which distinguishes the Orlando reference" (Office Action, page 20). The Examiner maintains that motivation to combine Orlando *et al.* and Hacia *et al.* is provided because use of fluorescent dyes of Hacia *et al.* "permits replacement of the radioactive components used in Orlando and avoidance of radioactivity is desirable" and solves "Orlando's concern regarding background and specificity" (Office Action, page 21).

Applicants respectfully disagree. As noted above, the claims have been amended to indicate that the DNA fragments are combined with a DNA microarray comprising one or more sequences complementary to one or more intergenic regions of genomic DNA of the cell ***wherein each one or more sequences is located at a particular spot on the DNA microarray*** and the one or more intergenic regions are upstream of transcribed regions of the genomic DNA.

Orlando *et al.* teach "a PCR and hybridization strategy that allows the identification of all binding sites of ***a particular protein*** within a genomic region of interest. DNA associated with specifically immunopurified chromatin is amplified by PCR and used ***as a probe in a Southern analysis*** of a given genomic region" (Orlando *et al.*, page 205, column 2, emphasis added). Orlando *et al.* do not teach or suggest the use of a DNA microarray in their PCR and hybridization strategy, and thus, do not teach or suggest methods for modifying their PCR and hybridization strategy for doing so. In addition, Orlando *et al.* do not even suggest that the PCR and hybridization strategy can be used to identify regions across a genome of a cell where binding of ***DNA proteins*** occur (Claims 71-86).

Hacia *et al.* teach that replacing "a phycoerythrin-streptavidin conjugate which produces fluorescein (green) and phycoerythrin (red) hybridization signals" with a "two color red (phycoerythrin) and far-red (phycoerythrin•cy5) dye system" provides "more evenly matched signal intensities and deceased spectral overlap between the two fluorophores" in a mutational analysis of the 3.43 kb exon 11 of the hereditary breast and ovarian cancer gene *BRAC1* (Hacia *et al.*, page 3865, abstract, column 2). Hacia *et al.* do not teach or suggest use of the two dye system in a method to identify a region of a genome of a cell to which a protein of interest binds or to non-specifically amplify DNA fragments from the entire genome of a cell.

Orlando *et al.* note that determining the level at which hybridization rises above background is problematic, and teach that:

> For regions where the enrichment is large (for example in Polycomb immunoprecipitations), this background becomes negligible; however, the signal-to-background ratio may become significant in cases where a particular sequence is only weakly enriched during the immunoprecipitation. For example, if genomic DNA is hybridized for long periods to the genomic walk, a uniform hybridization of all bands may be seen (Orlando *et al.*, page 213, column 1).

As stated in the previously filed Amendment, Orlando *et al.* suggest a "number of solutions to this problem" (Orlando *et al.*, page 213, column 1), none of which involve the use of DNA microarrays. Orlando *et al.* further note that "repetitive elements will always hybridize strongly" and that in "these cases the signal resulting from specific immunoprecipitation cannot be accurately determined" (Orlando *et al.*, page 213, columns 1-2). Use of the two color system of Hacia *et al.* would not address the repetitive elements issue.

Orlando *et al.* also teach that "the hybridization profiles that are generated over extended genomic regions . . . reflect the fact that a three-dimensional, higher order structure was cross-linked" which is an indication that "an immunoprecipitated fragment might not necessarily represent a directly interacting DNA partner of the protein but could also cover a distant site which was in contact through the multimeric protein interactions of the chromatin structures" (Orlando *et al.*, page 214, column 1). Use of the two color system of Hacia *et al.* would also not address this issue.

Thus, one of skill in the art would not be motivated to combine the teachings of Orlando *et al.* and Hacia *et al.*, based on Orlando's recommendations for overcoming the background

problem of their PCR and hybridization strategy, none of which involve the use of DNA microarrays, and the other problems associated with their PCR and hybridization strategy that would not be overcome with the use a DNA microarray. Applicants maintain that the prior art combination of record has been made with the advantage of impermissible hindsight, and thus, the rejection is legally improper. That is, in making the obviousness rejection, the Examiner has read the prior art with the benefit of Applicants' disclosure in which there is a clear teaching of the desirability of using a DNA microarray to identify a region of a genome of a cell to which a protein of interest binds.

As for newly added Claims 77 and 78, the teachings of Orlando *et al.* and Hacia *et al.*, either alone or in combination, do not even suggest that the PCR and hybridization strategy can be used to identify regions across a genome of a cell where binding of ***DNA proteins*** occur.

The combined teaching of the Orlando *et al.* and Hacia *et al.* references do not render obvious Applicants' claimed invention, particularly as amended.

Rejection of Claims 23, 24, 37, 38, 54, 55, 69, 70, 85 and 86 under 35 U.S.C. §103(a)

Claims 23, 24, 37, 38, 54, 55, 69, 70, 85 and 86 are rejected under 35 U.S.C. §103(a) as being unpatentable over Orlando *et al.* in view of Hacia *et al.* and further in view of Hallahan *et al.* (Office Action, page 13).

Applicants respectfully disagree. As indicated above, the combined teaching of Orlando *et al.* and Hacia *et al.* do not render obvious Applicants' claimed method. Hallahan *et al.* do not cure the deficiencies of the Orlando *et al.* and Hacia *et al.* references.

Hallahan *et al.* studied the role of the immediate early genes, *c-jun* and *Egr-1* "in cell cycle kinetics and cell survival following x-ray irradiation of clones containing inducible dominant negatives to *c-jun* and *Egr-1*" (Hallahan *et al.*, abstract). Hallahan *et al.* show that "the dominant negatives to the stress-inducible immediate early genes *Egr-1* and *c-jun* prevent the onset of S phase and reduce the survival of human cells exposed to ionizing radiation" (Hallahan *et al.*, abstract).

The combined teaching of the Orlando *et al.*, Hacia *et al.* and Hallahan *et al.* references do not render obvious Applicants' claimed invention, particularly as amended.

Rejection of claims 23, 24, 37, 38, 54, 55, 69, 70, 85 and 86 under 35 U.S.C. §103(a)

Claims 23, 24, 37, 38, 54, 55, 69, 70, 85 and 86 are rejected under 35 U.S.C. §103(a) as being unpatentable over Mercola in view of Hallahan *et al.* (Office Action, page 14).

Applicants respectfully disagree. Mercola *et al.* do not teach a method of identifying a region of a genome of a cell to which a protein of interest binds comprising, *inter alia*, combining a DNA fragment to which a protein of interest binds with a DNA microarray, wherein the DNA microarray comprises one or more sequences complementary to one or more ***intergenic regions*** of genomic DNA and *the one or more intergenic regions are upstream of transcribed regions of the genomic DNA,* under conditions in which hybridization occurs, and identifying the ***intergenic region*** to which the DNA fragment hybridizes. Hallahan *et al.* do not cure the deficiency of the Mercola *et al.* reference.

As discussed above, Hallahan *et al.* show that "the dominant negatives to the stress-inducible immediate early genes *Egr-1* and *c-jun* prevent the onset of S phase and reduce the survival of human cells exposed to ionizing radiation" (Hallahan *et al.*, abstract).

The combined teaching of the Mercola *et al.* and Hallahan *et al.* references do not render obvious Applicants' claimed invention, particularly as amended.

Rejection of Claims 1-6, 8-11, 15-26, 28-43, 45-59 and 61-86 under the judicially created doctrine of obviousness-type double patenting

Claims 1-6, 8-11, 15-26, 28-43, 45-59 and 61-86 "are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-11 of U.S. Patent No. 6,410,243 in view of Hacia and further in view of Hallahan" (Office Action, page 15).

As indicated in the previously filed Amendment, Applicants will address the double patenting rejection when it is the only remaining rejection in the subject application.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

By Anne J Collins

Anne J. Collins, Registration No. 40,564
On behalf of Herbert R. Schulze, Registration No. 30,682
Telephone: (978) 341-0036
Facsimile: (978) 341-0136

Concord, MA 01742-9133
Dated: March 3, 2006